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This Month in *AJP*

Imaging Lymph Node Lymphangiogenesis

The expansion of lymphatic networks (ie, lymphangiogenesis) within tumor-draining lymph nodes might be the earliest sign of metastasis. However, detection of residual inflammation-induced lymph node lymphangiogenesis might hamper the identification of metastasized lymph nodes. Therefore, Mumprecht et al (**Am J Pathol 2012, 180:874–879**) investigated whether lymphatic vessels in the lymph nodes regress on resolution of inflammation in a mouse model of skin inflammation. Lymph node lymphangiogenesis was identified using radiolabeled antibodies against the lymphatic vessel endothelial hyaluronan receptor-1 (LYVE-1) and visualized with positron emission tomography (PET). This technique, termed anti–LYVE-1 immuno-PET, was very sensitive in detecting lymph node metastasis. The data revealed that the lymphatic network regressed on resolution of inflammation. Such imaging of lymphatic vessel expansion in lymph nodes might be a promising strategy for the early detection of cancer metastasis.

c-Rel Stimulates Cardiac Hypertrophy

NF-κB activity is increased in the diseased heart, but how its individual subunits contribute to cardiovascular disease is not understood. Gaspar-Pereira et al (**Am J Pathol 2012, 180:929–939**) assign a new role for the c-Rel subunit as a stimulator of cardiac hypertrophy and fibrosis. c-Rel–deficient mice had smaller hearts and were protected from developing cardiac hypertrophy and fibrosis after chronic angiotensin infusion. Transcriptional activators of hypertrophy, myocyte enhancer family, Gata4, and Tbx proteins were identified as c-Rel gene targets. Overexpression of the p50 subunit in H9c2 cells repressed c-Rel levels, and the absence of cardiac p50 was associated with increases in both c-Rel levels and cardiac hypertrophy. Thus, c-Rel–dependent signaling is critical for both cardiac remodeling and hypertrophy, and targeting its activities could offer a novel therapeutic strategy to limit the effects of cardiac disease.

Stress Induces Premature Senescence

Stress-induced premature senescence (SIPS) of endothelial cells contributes to global endothelial cell dysfunction, including lysosomal dysfunction. Chen et al (**Am J Pathol 2012, 180:973–983**) examined the impact of a range of cardiovascular risk factors on the expression of sirtuin 1 (SIRT1), SIPS, and apoptosis. The effects of stressors could be partially mimicked by inducing lysosomal membrane permeabilization or inhibiting autophagy and were reversed by a cathepsin inhibitor. SIRT1 is an important substrate of cysteine cathepsins B, S, and L, and the antioxidant/peroxynitrite scavenger ebselen prevented stress-induced SIRT1 depletion and subversion of autophagy by mitigating lysosomal dysfunction. These data advance the concept of "stem cell aging" by establishing the critical role of lysosomal dysfunction and linking cell stress to apoptosis and SIPS.

Enterovirus Infection and CNS Developmental Defects

Coxsackievirus B3 (CVB3) can persist within the neonatal central nervous system (CNS) and target neural stem cells. Given that CVB3 is a cytolytic virus, Ruller et al (**Am J Pathol 2012, 180:1107–1120**) characterized the potential reduction in neurogenesis within the developing brain and the subsequent developmental defects. Neonatal mice inoculated with a recombinant CVB3 exhibited a reduction in proliferating cells in CNS neurogenic regions together with the presence of apoptosis. A permanent decrease in brain wet weight was also observed, along with signs of astrogliosis and compaction of the cortical layers. Intriguingly, partial brain wet weight recovery was observed in mice treated with the antiviral drug ribavirin during the persistent stage of infection. Hence, long-term neurological sequelae might be expected after neonatal enteroviral infections, yet antiviral treatment initiated long after the end of acute infection might limit virus-mediated neuropathology.

Heterogeneity of TECs

Tumor endothelial cells (TECs) differ from normal endothelial cells, but whether the characteristics of TECs derived from different tumors differ remains unknown. To elucidate this, Ohga et al (**Am J Pathol 2012, 180:1294–1307**) isolated TECs from high metastatic (HM-TECs) and low metastatic (LM-TECs) tumors and compared their characteristics. HM-TECs showed higher proliferative activity and invasive activity than LM-TECs. Moreover, the mRNA expression levels of proangiogenic genes *VEGFR1*, *VEGFR2*, *VEGF*, and *HIF1A* as well as *SCA1* and *CD90* were higher in HM-TECs than in LM-TECs. HM-TECs differentiated into osteogenic cells, expressing activated alkaline phosphatase in an osteogenic medium at a higher rate than either LM-TECs or normal endothelial cells. These results indicate that TECs from HM tumors have a more proangiogenic phenotype than those from LM tumors. Further studies on TEC heterogeneity will facilitate the selection of suitable anti-angiogenic therapies.